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Award Number: W81XWH-10-2-0088

TITLE: Advanced MRI in Acute Military TBI

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REPORT DATE: September 2011

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release; distribution unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
01-09-2011	Annual	1 SEP 2010 - 31 AUG 2011

4. TITLE AND SUBTITLE

Advanced MRI in Acute Military TBI

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-10-2-0088

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Washington University
Saint Louis, MO 63130

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The objective of the project is to test two advanced MRI methods, DTI and resting-state fMRI correlation analysis, in military TBI patients acutely after injury and correlate findings with TBI-related clinical outcomes 6-12 months later. An additional objective is to test the interaction of candidate genetic vulnerability factors with patterns of injury. These combined methods may add clinically useful predictive information following traumatic brain injury that could be of assistance in standardizing diagnostic criteria for TBI, making return-to-duty triage decisions, guiding post-injury rehabilitation, and developing novel therapeutics. The overarching hypothesis is that traumatic axonal injury, interacting with genetic vulnerability factors, is a principal cause of impaired brain function following blast-related and non-blast-related TBI. The study is a prospective longitudinal study with subject enrollment and initial evaluation at Landstuhl Regional Medical Center in Landstuhl Germany. Follow-up evaluations are performed at Washington University in St Louis. To date, 129 subjects have been enrolled and 37 complete follow-up evaluations have been performed. There have been no adverse events.

15. SUBJECT TERMS

Traumatic Brain Injury. Blast. MRI. Diffusion Tensor Imaging. Post-traumatic Stress Disorder

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	7	19b. TELEPHONE NUMBER *(include area code)*

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Introduction

The objective of the project is to test two advanced MRI methods, DTI and resting-state fMRI correlation analysis, in military TBI patients acutely after injury and correlate findings with TBI-related clinical outcomes 6-12 months later. The interaction of candidate genetic vulnerability factors with patterns of injury will be evaluated. These combined methods may add clinically useful predictive information following traumatic brain injury that could be of assistance in standardizing diagnostic criteria for TBI, making return-to-duty triage decisions, guiding post-injury rehabilitation, and developing novel therapeutics.
The overarching hypothesis is that traumatic axonal injury, interacting with genetic vulnerability factors, is a principal cause of impaired brain function following blast-related and non-blast-related TBI.

The specific aims of the proposal are as follows:

Aim 1) To determine whether DTI and fcMRI will noninvasively reveal abnormalities that are not present on CT or conventional MRI acutely following blast-related and non-blast-related TBI. For this aim, a total of 200 participants with TBI, 100 with blast-related injuries and 100 with non-blast-related injuries, will be recruited at LRMC over a 2 year period.

Aim 2) To assess the frequency of clinically occult traumatic axonal injury resulting from blast and non-blast mechanisms that is detectible using DTI, fcMRI, and conventional MRI. For this aim, a total of 200 participants without TBI but with other injuries will be recruited at LRMC during the same 2 year period: 100 with blast-related injuries and 100 with non-blast-related injuries.

Aim 3) To use DTI and fcMRI to clarify the principal similarities and differences between blast-related TBI and TBI due to other mechanisms (e.g. motor vehicle accidents, falls, and direct blows to the head). This will be analyzed using the same 4 groups of participants described above in aims 1 and 2.

Aim 4) To test the hypothesis that specific pattern of injuries detected with these methods will predict specific longer-term neurological and neuropsychological deficits. We will collect detailed clinical information on TBI-related outcomes 6-12 months after injury at Washington University. This will include standardized neurobehavioral assessments, neuropsychological testing, and structured interviews for depression and post-traumatic stress disorder. Several pre-specified hypotheses based on known brain anatomical-clinical correlations will be tested. Also, exploratory approaches will be used as the structural bases for many post-traumatic deficits and disorders are not well understood.

Aim 5) To test the hypothesis that specific genetic factors interact with patterns of injuries to further increase the risk of specific neurological, neuropsychological, and psychiatric deficits and disorders. At follow-up, blood will be drawn for genetic testing. Genetic testing will be performed for *GABRA2* and *FKBP5* polymorphisms associated with PTSD, *5-HTTLPR* polymorphisms associated with increased risk of depression and PTSD following stressors, and *APOE* and *IL1β* genotypes associated with poor recovery from TBI.

Body

During the first year of the project, we have made substantial progress towards these aims. We trained clinical coordinators and MRI technologists at Landstuhl regional medical center (LRMC). We have enrolled a total of 129 subjects at LRMC as of August 30, 2011 (**Table 1**).

Group	Number of Subjects Enrolled
A: Blast exposed active-duty US military controls (no TBI)	15
B: Blast-related active-duty US military TBI subjects	48
C: Non-blast-exposed active-duty US military controls (no TBI)	36
D: Non-blast-related active-duty US military TBI subjects	30

There have been no adverse events. All acute DTI, fcMRI and conventional MRI scans performed using the new Siemens 3T scanner at LRMC have been of good quality. We have been allotted 1-2 scans per working day on the scanner. We are in the process of negotiating with the LRMC radiology group to obtain more scanner time; on several occasions, there were more potential subjects willing to participate, but insufficient scanner time available. We have successfully transferred MRI data and clinical information to Washington University without breaches of HIPAA regulations or other disclosure of confidential information. We have obtained a Medweb server and resolved all of the firewall permissions issues required to facilitate this process.

Dr. Ray Fang served as the LRMC site PI through July 4, 2011. Dr. John Oh served briefly as site PI. Currently, Dr. David Zonies has taken over as site PI.

LMRC had an audit by the ERMC AHRPO group. There were small protocol changes regarding record keeping, IRB documentation and HIPAA compliance recommended but no substantial scientific or ethical concerns were raised.

The PI performed a site visit at LRMC in June, 2011. No concerns were raised.

As of Oct 6, 2011, our LRMC site clinical coordinator will be leaving LRMC. We have trained a short-term replacement coordinator. We have identified a new longer-term coordinator and we are in the process of training him. Based on changes in the staffing level at LRMC, it will be most appropriate for the study to pay the salary of the LRMC site research coordinator. In the initial proposal, the LRMC site coordinator salary was paid by LRMC. We have applied for additional funds from CDRMP to support the LRMC site coordinator.

We have performed telephone-based monthly clinical assessments and began scheduling in-person follow-up evaluations in St Louis. We have recruited and trained a team of psychometricians and clinical psychologists to perform the in-person neuropsychological and psychiatric evaluations. We have performed 37 of these in-person evaluations since April, 2011. Others have been scheduled through 2012. There have been no complications arising from the evaluations. All subjects have been able to complete transportation in and out of St. Louis. No adverse effects of repeat MRI scans, neuropsychological testing, and psychiatric evaluations have been observed.

Initially, there was a low rate of consent for participation in the genetics portion of the study (which is optional: subjects can participate in the overall study but opt out of the genetics portion). This was determined to be due to the blood draw component. Therefore, with IRB approval, we have switched our method of collection from blood to saliva. Since then, we have had many fewer subjects refusing to participate in the genetics portion. We plan to request IRB approval to re-contact subjects who have already been evaluated but declined genetics assessments and ask them to consider sending a saliva sample by Fedex. In this way, we hope to optimize the sample size for Aim 5. We have run the PCR-based genetic polymorphisms on the samples from the first 10 subjects. Most were technically successful. We are optimizing conditions for the others.

We have hired a post-doctoral fellow, Dr. Kihwan Han, to assist with the analysis of the fcMRI data and develop new methods for DTI analysis. He has been making good progress.

The PI served as an advisor to GEN Chiarrelli and ADM Dunfort at the Blue Ribbon Symposium held in Bethesda in Dec 2010 regarding imaging of blast-related TBI.

The PI served as an assistant to COL Chris Macedonia, medical advisor to ADM Mullins, during the Gray Team visit to Afghanistan in January, 2011. Our experience from the current study was used to help address logistical issues surrounding the plan to place two MRI scanners in Afghanistan for both clinical and research use.

The PI has drawn upon his experience with the current study to help Dr. Octavian Adam plan an acute MRI study of blast-related TBI patients based in Kandahar.

The research group has presented related findings from the related study PT072599 at several national and international meetings. Initial results have been published in *The New England Journal of Medicine*.

Key Research Accomplishments:

-Enrollment of 129 subjects at LRMC from all 4 planned groups.

-Completion of 37 in-person follow-up evaluations in St Louis.

Reportable Outcomes from the Current Project:
None.

Reportable outcomes from the closely-related study PT072599:

Papers:
C.L. Mac Donald, A.M. Johnson, D. Cooper, E. C. Nelson, N. J. Werner, J. S. Shimony, A. Z. Snyder, M. E. Raichle, J. R. Witherow, R. Fang, S. F. Flaherty, and D. L. Brody "Detection of Blast-Related Traumatic Brain Injury in US Military Personnel" New England Journal of Medicine 2011: 364: 2091-2100.

Abstracts and Presentations:
The PI and Dr. Mac Donald presented aspects of the results at several meetings and seminars:

1. 2011 ATACCC meeting. (The PI won the first prize award for poster presentation)
2. 2011 Research Seminar at The Ospedale Maggiore Policlinico, University of Milan, Italy
3. 2011 National Neurotrauma Society Meeting
4. 2011 International Society for Magnetic Resonance in Medicine (ISMRM) meeting.
5. 2011 International Neurotrauma Society Meeting
6. 2011 Safar Symposium, University of Pittsburgh
7. 2011 MIT Blast-injury Modeling Symposium
8. 2010 Army Vice Chief of Staff Blue Ribbon Symposium on TBI and PTSD
9. 2010 Society for Neuroscience Meeting

Conclusion:

The study is proceeding according to the proposed plan. No major roadblocks have been encountered. Overall, recruitment is proceeding well. We had hoped to have recruited 200 subjects by the end of the first year. The main area of slow recruitment has been in blast-exposed controls without TBI (group A). We will focus on recruiting subjects from this group during the next recruiting period.

References:

Mac Donald et al, NEJM 2011 (attached).

Appendices: None.